M-I (1) Scientific Abstract. Cardiovascular disease is the single leading cause of mortality in the United States, responsible for the deaths of two out of every five Americans, with total of nearly one million deaths annually. Coronary artery disease describes a broad spectrum of ischemic syndromes that may evolve from artherosclerosis, thrombosis, and/or vasospasm. Current therapies include pharmacologic interventions and surgical therapy by mechanical revascularization using percutaneous transluminal coronary angioplasty, coronary artery bypass grafting or transmyocardial laser revascularization. The identification of specific biologic mediators of angiogenesis make it possible to consider "therapeutic angiogenesis," where angiogenic molecules can be employed to develop new vascular networks to circumvent the ischemic consequences of artherosclerosis occluding the arterial system. The most specific of the known angiogenic indicators is vascular endothelial growth factor (VEGF). The focus of this protocol is to determine the safety/toxicity and biologic efficacy of the delivery of VEGF cDNA directly into the myocardium of individuals with life threatening coronary artery disease via a catheter based approach. The protocol will use a vector similar to the Ad vector which has been safely administered to the myocardium of 31 individuals, including 25 individuals at the same or higher doses (RAC #9711-221 and RAC #9806-258). The vector to be used is a E1- and E3-adenovirus gene transfer vector expressing vascular endothelial growth factor under cytomegalovirus early/intermediate promoter/enhancer. Following administration of the Ad_{CU}VEGF.1 vector into the heart there will be assessment of exercise tolerance and myocardial blood flow by using a positron emission tomography (PET) scan. The study will involve 10 individuals, each with clinically significant coronary artery disease, who, in the opinion of their cardiologist, are not optimal candidates for coronary artery bypass graft surgery or percutaneous coronary intervention (PCI) i.e., balloon, stent, atherectomy. At the conclusion of the study, the following objective will be met: (1) to determine the safety/toxicity of direct administration of the vector Ad_{CU}VEGF.1 to the ischemic myocardium, using a non-surgical catheter-based approach; (2) to assess whether direct administration of Ad_{CU}VEGF.1 to the myocardium will induce growth of collateral blood vessels, improve coronary blood flow and improve cardiac function in the region of ischemia.